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☐ 1. Document ID: US 20030013691 A1 Relevance Rank: 99

L3: Entry 6 of 10 File: PGPB Jan 16, 2003

PGPUB-DOCUMENT-NUMBER: 20030013691
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DOCUMENT-IDENTIFIER: US 20030013691 A1

TITLE: 2-ethyl and 2-ethylidene-19-nor-vitamin D compounds

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☑ 2. Document ID: US 6806262 B2 Relevance Rank: 95

L3: Entry 8 of 10 File: USPT Oct 19, 2004

DOCUMENT-IDENTIFIER: US 6806262 B2
TITLE: 2-ethyl and 2-ethylidene-19-nor-vitamin D compounds

Abstract Text (1):
Biologically active 19-nor vitamin D analogs substituted at C-2 in the A-ring with an ethylidene or an ethyl group. These compounds have preferential activity on mobilizing calcium from bone and either high or normal intestinal calcium transport activity which allows their in vivo administration for the treatment of metabolic bone diseases where bone loss is a major concern. These compounds are also characterized by high cell differentiation activity.

INVENTOR (2):
Sicinski; Rafal R.

Inventor Group (2):
Sicinski; Rafal R. Warsaw PL

Brief Summary Text (10):
In a continuing search for biologically active vitamin D compounds novel 19-nor analogs of 1, substituted at C-2 with ethylidene (4a,b and 5a,b) and ethyl (6a,b and 7a,b) groups, have now been synthesized and tested. Structurally the novel 2-ethylidene analogs belong to a class of 19-nor vitamin D compounds characterized by the general formula I shown below: ##STR1##

Brief Summary Text (20):

The above novel compounds exhibit a desired, and highly advantageous, pattern of biological activity. The synthesized vitamins were tested for their ability to bind the porcine intestinal vitamin D receptor. The presented results (FIG. 5) indicate that 2-ethylidene-19-norvitamins, possessing methyl group from ethylidene moiety directed toward C-3, i.e., trans in relation to C(6)--C(7) bond (isomers E), are more active than 1.alpha.,25--(OH).sub.2 D.sub.3 in binding to VDR, whereas their counterparts with cis relationship between ethylidene methyl substituent and C(7)--H group (isomers Z) exhibit significantly reduced affinity for the receptor. The competitive binding analysis showed also that 2.alpha.-ethyl-19-norvitamins bind to the receptor better than their isomers with 2.beta.-ethyl substituents (FIG. 6). In the next assay, the cellular activity of the synthesized compounds was established by studying their ability to induce differentiation of human promyelocyte HL-60 cells into monocytes. E isomer of (20S)-2-ethylidene-19-nor-vitamin D.sub.3 (FIG. 7) and both 2.alpha.-ethyl-19-norvitamins (FIG. 8) are more potent than 1.alpha.,25--(OH).sub.2 D.sub.3 in this assay, whereas the remaining tested compounds are almost equivalent to the hormone 1. Both E isomers of 2-ethylidene-19-norvitamins, when tested in vivo in rats (Table 1) exhibited very high calcemic activity, the (20S)-compound being especially potent. On the contrary, isomeric Z compounds are significantly less active. 2-Ethyl-19-norvitamins have some ability to mobilize calcium from bone but not to the extent of the hormone 1, while being inactive in intestine. The only exception is the 2.alpha.-ethyl isomer from the 20S-series which shows strong calcium mobilization response and marked intestinal activity.

Brief Summary Text (25):
This invention also provides a novel synthesis for the production of the end products of structures I and II. Two different synthetic paths were devised, both based on Lythgoe type Wittig-Homer coupling of the A-ring fragments, the corresponding phosphine oxides prepared from quinic acid, with the protected 25-hydroxy Grundmann's ketone. In the first method, the allylic phosphine oxides were substituted at C-4' with the ethylidene group whereas in the alternative approach the introduction of ethylidene moiety was performed in the final step of the synthesis, by Wittig reaction of the intermediate 2-oxo-vitamin D analog. The selective catalytic hydrogenation of 2-ethylidene analogs of 1.alpha.,25-dihydroxy-19-norvitamin D.sub.3 provided the corresponding 2.alpha.- and 2.beta.-ethyl compounds.

Drawing Description Text (2):
FIG. 1 illustrates the general structural formulae for 1.alpha.,25-dihydroxyvitamin D.sub.3, 1.alpha.,25-dihydroxy-2-methylene-19-norvitamin D.sub.3, and 1.alpha.,25-dihydroxy-2.alpha.-methyl-19-norvitamin D.sub.3, and further illustrates the general structural formulae for the four 2-ethylidene-19-nor-vitamins and the four 2-ethyl-19-nor-vitamins of the present invention synthesized and tested herein;

Drawing Description Text (3):
FIG. 2 illustrates the configurations and preferred conformations of the 4'-ethylidene intermediates 16 and 17 used in the synthesis disclosed herein;

Drawing Description Text (6):
FIG. 3c illustrates that a strong interaction (designated as A.sup.(1,3) -strain) exists between the methyl group from the ethylidene moiety and equatorial hydroxyls at C-1 or C-3, and results in a strong bias toward conformers with an axial orientation of this hydroxy group to which the methyl from ethylidene fragment is directed; and

Drawing Description Text (8):
FIG. 5a is a graph illustrating the relative activity of a 2-ethylidene-19-nor-vitamins (isomers E and Z) and 1.alpha.,25-dihydroxyvitamin D.sub.3 to compete for binding of [.sup.3 H]-1,25-(OH).sub.2 -D.sub.3 to the pig intestinal nuclear vitamin D receptor;

Drawing Description Text (10):
FIG. 6a is a graph illustrating the percent HL-60 cell differentiation as a function of the concentration of the 2-ethylidene-19-nor-vitamins as compared to 1.alpha.,25-dihydroxyvitamin D.sub.3 ; and

Detailed Description Text (5):
In the following lists of compounds, the particular isometric form of the ethylidene substituent attached at the carbon 2 position should be added to the nomenclature. For example, if the methyl group of the ethylidene substituent is in its (E) configuration, then the term "2(E)" should be included in each of the named compounds. If the methyl group of the ethylidene substituent is in its (Z) configuration, then the term "2(Z)" should be included in each of the named compounds. In addition, if the methyl group attached at the carbon 20 position is in its epi or unnatural configuration, the term "20(S)" or "20-epi" should be included in each of the following named compounds. Also, if the side chain contains an oxygen atom substituted at any of positions 20, 22 or 23, the term "20-oxa", "22-oxa" or "23-oxa", respectively, should be added to the named compound. The named compounds could also be of the vitamin D.sub.2 or D.sub.4 type if desired.

Detailed Description Text (6):
Specific and preferred examples of the 2-ethylidene-compounds of structure I when the side chain is unsaturated are:

Detailed Description Text (7):
2-ethylidene-19-nor-1,25-dihydroxy-22,23-dehydrovitamin D.sub.3 ;

Detailed Description Text (8):
2-ethylidene-19-nor-24-homo-1,25-dihydroxy-22,23-dehydrovitamin D.sub.3 ;

Detailed Description Text (9):
2-ethylidene-19-nor-24-dihomo-1,25-dihydroxy-22,23-dehydrovitamin D.sub.3 ;

Detailed Description Text (10):
2-ethylidene-19-nor-24-trihomo-1,25-dihydroxy-22,23-dehydrovitamin D.sub.3 ;

Detailed Description Text (11):
2-ethylidene-19-nor-26,27-dimethyl-24-homo-1,25-dihydroxy-22,23-dehydro vita min D.sub.3 ;

Detailed Description Text (12):
2-ethylidene-19-nor-26,27-dimethyl-24-dihomo-1,25-dihydroxy-22,23-dehyd rovi tamin D.sub.3 ;

Detailed Description Text (13):
2-ethylidene-19-nor-26,27-dimethyl-24-trihomo-1,25-dihydroxy-22,23-dehy drov itamin D.sub.3 ;

Detailed Description Text (14):
2-ethylidene-19-nor-26,27-diethyl-24-homo-1,25-dihydroxy-22,23-dehydrov itam in D.sub.3 ;

Detailed Description Text (15):
2-ethylidene-19-nor-26,27-diethyl-24-dihomo-1,25-dihydroxy-22,23-dehydr ovit amin D.sub.3 ;

Detailed Description Text (16):
2-ethylidene-19-nor-26,27-diethyl-24-trihomo-1,25-dihydroxy-22,23-dehyd rovi tamin D.sub.3 ;

Detailed Description Text (17):
2-ethylidene-19-nor-26,27-dipropoyl-24-homo-1,25-dihydroxy-22,23-dehydr ovit amin D.sub.3 ;

Detailed Description Text (18):
2-ethylidene-19-nor-26,27-dipropyl-24-dihomo-1,25-dihydroxy-22,23-dehyd rovi tamin D.sub.3 ; and

Detailed Description Text (19):
2-ethylidene-19-nor-26,27-dipropyl-24-trihomo-1,25-dihydroxy-22,23-dehy drov itamin D.sub.3.

Detailed Description Text (20):
With respect to the above unsaturated compounds, it should be noted that the double bond located between the 22 and 23 carbon atoms in the side chain may be in either the (E) or (Z) configuration. Accordingly, depending upon the configuration, the term "22,23(E)" or "22,23(Z)" should be included in each of the above named compounds. Also, it is common to designate the double bond located between the 22 and 23 carbon atoms with the designation ".DELTA..sup.22 ". Thus, for example, the first named compound above could also be written as 2-ethylidene-19-nor-22,23(E)-.DELTA..sup.22 -1,25--(OH).sub.2 D.sub.3 where the double bond is in the (E) configuration. Similarly, if the methyl group attached at carbon 20 is in the unnatural configuration, this compound could be written as 2-ethylidene-19-nor-20(S)-22,23(E)-.DELTA..sup.22 -1,25--(OH).sub.2 D.sub.3.

Detailed Description Text (21):
Specific and preferred examples of the 2-ethylidene-compounds of structure I when the side chain is saturated are:

Detailed Description Text (22):
2-ethylidene-19-nor-1,25-dihydroxyvitamin D.sub.3 ;

Detailed Description Text (23):
2-ethylidene-19-nor-24-homo-1,25-dihydroxyvitamin D.sub.3 ;

Detailed Description Text (24):
2-ethylidene-19-nor-24-dihomo-1,25-dihydroxyvitamin D.sub.3 ;

Detailed Description Text (25):
2-ethylidene-19-nor-24-trihomo-1,25-dihydroxyvitamin D.sub.3 ;

Detailed Description Text (26):
2-ethylidene-19-nor-26,27-dimethyl-24-homo-1,25-dihydroxyvitamin D.sub.3 ;

Detailed Description Text (27):
2-ethylidene-19-nor-26,27-dimethyl-24-dihomo-1,25-dihydroxyvitamin D.sub.3 ;

Detailed Description Text (28):
2-ethylidene-19-nor-26,27-dimethyl-24-trihomo-1,25-dihydroxyvitamin D.sub.3 ;

Detailed Description Text (29):
2-ethylidene-19-nor-26,27-diethyl-24-homo-1,25-dihydroxyvitamin D.sub.3 ;

Detailed Description Text (30):
2-ethylidene-19-nor-26,27-diethyl-24-dihomo-1,25-dihydroxyvitamin D.sub.3 ;

Detailed Description Text (31):
2-ethylidene-19-nor-26,27-diethyl-24-trihomo-1,25-dihydroxyvitamin D.sub.3 ;

Detailed Description Text (32):

2-ethylidene-19-nor-26,27-dipropyl-24-homo-1,25-dihydroxyvitamin D.sub.3 ;

Detailed Description Text (33):
2-ethylidene-19-nor-26,27-dipropyl-24-dihomo-1,25-dihydroxyvitamin D.sub.3 ; and

Detailed Description Text (34):
2-ethylidene-19-nor-26,27-dipropyl-24-trihomo-1,25-dihydroxyvitamin D.sub.3.

Detailed Description Text (36):
19-nor-2(E)-ethylidene-1.alpha.,25-dihydroxyvitamin D.sub.3 ;

Detailed Description Text (37):
19-nor-2(Z)-ethylidene-1.alpha.,25-dihydroxyvitamin D.sub.3 ;

Detailed Description Text (38):
19-nor-2E)-ethylidene-20(S)-1.alpha.,25-dihydroxyvitamin D.sub.3 ; and

Detailed Description Text (39):
19-nor-2(Z)-ethylidene-20(S)-1.alpha.,25-dihydroxyvitamin D.sub.3.

Detailed Description Text (75):
The preparation of 2-ethylidene-9-nor-vitamin D compounds, and the 2-ethyl-19-nor-vitamin D compounds, having the basic structure I and II can be accomplished by a common general method, i.e. the condensation of a bicyclic Windaus-Grundmann type ketone III with the allylic phosphine oxide IVa or IVb to the corresponding 2-ethylidene-19-nor-vitamin D analogs Va or Vb, respectively followed by a selective reduction of the ethylidene group at C-2 to the corresponding 2-ethyl compounds. ##STR7##

Detailed Description Text (79):
Referring now to Scheme 2, the next step of the synthesis comprises the Wittig reaction of the sterically hindered 4-keto compound 13 with ylide prepared from ethyltriphenylphosphonium bromide and n-butyllithium leading to ethylidene compounds 14 and 15. Ethylidene compounds 14 and 15 in turn were treated with diisobutylaluminum hydride and the formed alcohols 16 and 17 were in turn transformed to the desired A-ring phosphine oxides 18 and 19. Conversion of 16 and 17, to 18 and 19, respectively involved 3 steps, namely, in situ tosylation with n-butyllithium and p-toluenesulfonyl chloride, followed by reaction with diphenylphosphine lithium salt and oxidation with hydrogen peroxide.

Detailed Description Text (80):
Several 2-ethylidene-19-nor-vitamin D compounds of the general structure V may be synthesized using the A-ring synthons 18 and 19 and the appropriate Windaus-Grundmann ketone III having the desired side chain structure. Thus, for example, Scheme 3 illustrates that Wittig-Horner coupling of the phosphinoxy 18 with the protected 25-hydroxy Grundmann's ketone 20 prepared according to published procedure [Sicinski et al., J. Med. Chem. 37, 3730 (1994)] gave the expected protected vitamin compound 21. This, after deprotection afforded 1.alpha.,25-dihydroxy-2(E)-ethylidene-19-nor-vitamin D.sub.3 (4a). Similarly, Scheme 3 illustrates the synthesis of 1.alpha.,25-dihydroxy-2(Z)-ethylidene-19-nor-vitamin D.sub.3 (5a) from phosphinoxy 19 and Grundmann's ketone 20.

Detailed Description Text (81):
Referring now to Scheme 6, the final step of the process was the selective homogeneous catalytic hydrogenation of the ethylidene unit at carbon 2 in the vitamins 4a and 5a performed efficiently in the presence of tris (triphenylphosphine)rhodium(I) chloride [Wilkinson's catalyst, (Ph.sub.3 P).sub.3 RhCl]. Such reduction conditions allowed to reduce only C(2).dbd.CH.sub.2 unit leaving C(5)--C(8) butadiene moiety unaffected. The isolated material is an epimeric mixture (ca. 1:1) of 2-ethyl-19-nor-vitamins 6a and 7a differing in

configuration at C-2. The mixture can be used without separation or, if desired, the individual 2.alpha.- and 2.beta.-isomers can be separated by an efficient HPLC system.

Detailed Description Text (82):
The C-20 epimerization may be accomplished by the analogous coupling of the phosphine oxides 18 and 19 with protected 20(S)-25-hydroxy Grundmann's ketone 26 (Scheme 5) which after hydrolysis of the hydroxy-protecting groups gave 20(S)-1.alpha.,25-dihydroxy-2-ethylidene-19-nor-vitamin D.sub.3 compounds 4b and 5b. Hydrogenation of 4b and 5b provided the expected mixture of the 2-ethyl-19-nor-vitamin D analogs 6b and 7b.

Detailed Description Text (83):
As noted above, other 2-ethylidene and 2-ethyl-19-nor-vitamin D analogs may be synthesized by the method disclosed herein. For example, 1.alpha.-hydroxy-2-ethylidene-19-nor-vitamin D.sub.3 can be obtained by providing the Grundmann's ketone (g). Subsequent reduction of the A-ring ethylidene group in the formed compound can also give the corresponding epimeric mixture of 1.alpha.-hydroxy-2-ethyl-19-nor-vitamin D.sub.3 compounds.

Detailed Description Text (88):
The strategy of the synthesis of 2-substituted 19-norvitamins was based on Lythgoe-type Wittig-Horner coupling. Since the corresponding C,D-ring ketones were available, attention was focused on the synthesis of the phosphine oxide A-ring synthons (Scheme 1 and 2). Configurations of the ethylidene unit at C'-4 in the isomeric compounds 16, 17 (FIG. 2) and 17, 18, as well as their preferred conformations, were determined by analysis of .sup.1 H NMR spectra, NOE measurements and spin decoupling experiments.

Detailed Description Text (89):
The Wittig-Homer reaction of the conjugate base of 20 with the protected 25-hydroxy Grundmann's ketone 20 produced 19-norvitamin D compound 21 in a very high yield, i.e. 91% (Scheme 3), but the yield of an analogous coupling of the isomeric phosphine oxide 19 was very low, i.e. 13%. The obtained condensation products 21 and 22, following deprotection, gave 2-ethylidene-19-norvitamins 4a and 5a. Considering the low yield of the Wittig reaction of the cyclohexanone 13, leading to ethylidene compounds 14 and 15 (Scheme 2), an alternative synthetic approach was sought.

Detailed Description Text (90):
Thus, the carbonyl group in 13 was protected as O-trimethylsilyl hemimethylthioketal and the corresponding phosphine oxides 25 were efficiently synthesized (Scheme 4). Coupling of their anions with the hydrindanone 26 (Scheme 5) afforded the protected 19-norvitamin D compound 27 in a high yield. This, after deprotection of 2-oxo group, Wittig reaction and subsequent hydrolysis was converted to (20S)-2-ethylidene-19-norvitamins 4b and 5b. The selective catalytic hydrogenation of 2-ethylidene analogs 4a, b and 5a, b (Scheme 6) provided the corresponding 2-ethyl-19-norvitamins 6a, b and 7a, b, which were easily separated by HPLC.

Detailed Description Text (94):
It has been established that vitamin D compounds in solutions exist as a mixture of two rapidly equilibrating A-ring chair conformers abbreviated as .alpha.- and .beta.-forms (FIG. 3a). Presence of bulky 2-alkyl substituents, characterized by large conformational free energy A values (FIG. 3b), shifts the A-ring conformational equilibrium of the synthesized 2-ethyl-19-norvitamins toward the conformers with the equatorial C(2)-substituents. In the obtained 2-ethylidene-19-norvitamin D compounds, an additional strong interaction (designated as A.sup.(1-3) -strain, FIG. 3c) is involved, existing between the methyl group from the ethylidene moiety and equatorial hydroxyls at C-1 or C-3. It results in the strong

bias toward conformers with an axial orientation of this hydroxy group to which the methyl from ethylidene fragment is directed.

Detailed Description Text (98):
The synthesized vitamins were tested for their ability to bind the porcine intestinal vitamin D receptor. The presented results (FIG. 5a) indicate that 2-ethylidene-19-norvitamins, possessing methyl group from ethylidene moiety directed toward C-3, i.e. trans in relation to C(6)--C(7) bond (isomers E), are more active than 1.alpha.,25-(OH).sub.2 D.sub.3 in binding to VDR, whereas their counterparts with cis relationship between ethylidene methyl substituent and C(7)-H group (isomers Z) exhibit significantly reduced affinity for the receptor. The competitive binding analysis showed also that 2.alpha.-ethyl-19-norvitamins bind the receptor better than their isomers with 20-ethyl substituents (FIG. 5b). In the next assay, the cellular activity of the synthesized compounds was established by studying their ability to induce differentiation of human promyelocyte HL-60 cells into monocytes. E isomer of (20S)-2-ethylidene-19-norvitamin D.sub.3 (FIG. 6a) and both 2.alpha.-ethyl-19-norvitamins (FIG. 6b) are more potent than 1.alpha., 25--(OH).sub.2 D.sub.3 in this assay, whereas the remaining tested compounds are almost equivalent to the hormone.

Detailed Description Text (99):
Both E isomers of 2-ethylidene-19-norvitamins, when tested in vivo in rats (Table 1) exhibited very high calcemic activity, the (20S)-compound being especially potent. On the contrary, isomeric Z compounds are significantly less active. 2-ethyl-19-norvitamins have some ability to mobilize calcium from bone but not to the extent of the hormone 1, while being inactive in intestine. The only exception is 2.alpha.-ethyl isomer from 20S-series that shows strong calcium mobilization response and marked intestinal activity.

Detailed Description Paragraph Table (1):
TABLE 1 Support of Intestinal Calcium Transport and Bone Calcium Mobilization By 2-Substituted Analogs of 1.alpha.,25-Dihydroxy-19- norvitamin D.sub.3 In Vitamin D-Deficient Rats on a Low-Calcium Diet.sup.a compd. amount Ca transport S/M Serum Ca compound no. (pmol) (mean .+-. SEM) (mean .+-. SEM) none (control) 0 3.0 .+-. 0.7 4.3 .+-. 0.1 1.alpha.,25-(OH).sub.2 D.sub.3 1 130 5.5 .+-. 0.5 5.1 .+-. 0.3 260 5.9 .+-. 0.4 5.8 .+-. 0.3 2-ethylidene-19- 4a 65 5.0 .+-. 0.4 4.5 .+-. 0.1 nor-1.alpha.,25- 130 6.8 .+-. 0.4 5.2 .+-. 0.2 (OH).sub.2 D.sub.3 (E-isomer) 2-ethylidene-19- 5a 65 4.4 .+-. 0.4 4.4 .+-. 0.2 nor-1.alpha.,25- 130 5.7 .+-. 0.9 4.2 .+-. 0.0 (OH).sub.2 D.sub.3 (Z-isomer) none (control) 0 4.4 .+-. 0.2 4.1 .+-. 0.2 1.alpha.,25-(OH).sub.2 D.sub.3 1 130 4.9 .+-. 0.7 5.2 .+-. 0.2 260 6.0 .+-. 0.9 6.4 .+-. 0.4 2-ethylidene-19- 4b 65 9.0 .+-. 0.3 8.2 .+-. 0.3 nor-(20S)-1.alpha.,25- 130 5.8 .+-. 0.8 12.1 .+-. 0.6 (OH).sub.2 D.sub.3 (E-isomer) 2-ethylidene-19- 5b 65 4.3 .+-. 0.7 4.0 .+-. 0.3 nor-(20S)-1.alpha.,25- 130 3.8 .+-. 0.3 4.0 .+-. 0.1 (OH).sub.2 D.sub.3 (Z-isomer) none (control) 0 3.8 .+-. 0.4 3.9 .+-. 0.1 1.alpha.,25-(OH).sub.2 D.sub.3 1 260 6.5 .+-. 0.9 5.8 .+-. 0.1 2.alpha.-ethyl-19-nor- 6a 260 4.0 .+-. 0.4 5.1 .+-. 0.1 1.alpha.,25-(OH).sub.2 D.sub.3 2.beta.-ethyl-19-nor- 7a 260 3.7 .+-. 0.3 5.0 .+-. 0.1 1.alpha.,25-(OH).sub.2 D.sub.3 2.alpha.-ethyl-19-nor- 6b 260 5.0 .+-. 0.4 7.0 .+-. 0.1 (20S-1.alpha.,25- (OH).sub.2 D.sub.3 2.beta.-ethyl-19-nor- 7b 260 4.1 .+-. 0.3 5.6 .+-. 0.1 (20S)-1.alpha.,25- (OH).sub.2 D.sub.3 .sup.a Weanling male rats were maintained on a 0.47% Ca diet for one week and then switched to a low-calcium diet containing 0.02% Ca for an additional three weeks. During the last week, they were dosed daily with the appropriate vitamin D compound for seven consecutive days. All doses were administered intraperitoneally in 0.1 mL propylene glycol/ethanol (95:5). Controls received the vehicle. Determinations were made 24 hours after the last dose. There were at least six rats per group.

Other Reference Publication (11):
Sicinski, Rafal R. et al, "New 1.alpha.,25-Dihydroxy-19-norvitamin D.sub.3 Compounds of High Biological Activity: Synthesis and Biological Evaluation of 2-

Hydroxymethyl, 2-Methyl, and 2-Methylene Analogues," J. Med. Chem., 1998, 41, pp. 4662-4672.

CLAIMS:

5. 19-nor-2(E)-ethylidene-1.alpha.,25-dihydroxyvitamin D.sub.3.

6. 19-nor-2(Z)-ethylidene-1.alpha.,25-dihydroxyvitamin D.sub.3.

7. 19-nor-2(E)-ethylidene-20(S)-1.alpha.,25-dihydroxyvitamin D.sub.3.

8. 19-nor-2(Z)-ethylidene-20(S)-1.alpha.,25-dihydroxyvitamin D.sub.3.

33. A pharmaceutical composition containing 19-nor-2(E)-ethylidene-1.alpha.,25-dihydroxyvitamin D.sub.3 together with a pharmaceutically acceptable excipient.

34. The pharmaceutical composition of claim 33 containing 19-nor-2(E)-ethylidene-1.alpha.,25-dihydroxyvitamin D.sub.3 in an amount from about 0.01 .mu.g to about 100 .mu.g per gram of the composition.

35. The pharmaceutical composition of claim 33 containing 19-nor-2(E)-ethylidene-1.alpha.,25-dihydroxyvitamin D.sub.3 in an amount from about 0.1 .mu.g to about 50 .mu.g per gram of the composition.

39. A pharmaceutical composition containing 19-nor-2(Z)-ethylidene-1.alpha.,25-dihydroxyvitamin D.sub.3 together with a pharmaceutically acceptable excipient.

40. The pharmaceutical composition of claim 39 containing 19-nor-2(Z)-ethylidene-1.alpha.,25-dihydroxyvitamin D.sub.3 in an amount from about 0.01 .mu.g to about 100 .mu.g per gram of the composition.

41. The pharmaceutical composition of claim 39 containing 19-nor-2(Z)-ethylidene-1.alpha.,25-dihydroxyvitamin D.sub.3 in an amount from about 0.1 .mu.g to about 50 .mu.g per gram of the composition.

45. A pharmaceutical composition containing 19-nor-2(E)-ethylidene-20(S)-1.alpha.,25-dihydroxyvitamin D.sub.3 together with a pharmaceutically acceptable excipient.

46. The pharmaceutical composition of claim 45 containing 19-nor-2(E)-ethylidene-20(S)-1.alpha.,25-dihydroxyvitamin D.sub.3 in an amount from about 0.01 .mu.g to about 100 .mu.g per gram of the composition.

47. The pharmaceutical composition of claim 45 containing 19-nor-2(E)-ethylidene-20(S)-1.alpha.,25-dihydroxyvitamin D.sub.3 in an amount from about 0.1 .mu.g to about 50 .mu.g per gram of the composition.

51. A pharmaceutical composition containing 19-nor-2(Z)-ethylidene-20(S)-1.alpha.,25-dihydroxyvitamin D.sub.3 together with a pharmaceutically acceptable excipient.

52. The pharmaceutical composition of claim 51 containing 19-nor-2(Z)-ethylidene-20(S)-1.alpha.,25-dihydroxyvitamin D.sub.3 in an amount from about 0.01 .mu.g to about 100 .mu.g per gram of the composition.

53. The pharmaceutical composition of claim 51 containing 19-nor-2(Z)-ethylidene-20(S)-1.alpha.,25-dihydroxyvitamin D.sub.3 in an amount from about 0.1 .mu.g to about 50 .mu.g per gram of the composition.

☑ 3. Document ID: US 6992074 B2 Relevance Rank: 94

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DOCUMENT-IDENTIFIER: US 6992074 B2
TITLE: 2-Ethyl and 2-ethylidene-19-nor-vitamin D compounds

PRIOR-PUBLICATION:

DOC-ID	DATE
US 20050043281 A1	February 24, 2005

Abstract Text (1):
Biologically active 19-nor vitamin D analogs substituted at C-2 in the A-ring with an ethylidene or an ethyl group. These compounds have preferential activity on mobilizing calcium from bone and either high or normal intestinal calcium transport activity which allows their in vivo administration for the treatment of metabolic bone diseases where bone loss is a major concern. These compounds are also characterized by high cell differentiation activity.

Inventor Name (2):
Sicinski; Rafal R.

Inventor Group (2):
Sicinski; Rafal R. Warsaw PL

Brief Summary Text (10):
In a continuing search for biologically active vitamin D compounds novel 19-nor analogs of 1, substituted at C-2 with ethylidene (4a,b and 5a,b) and ethyl (6a,b and 7a,b) groups, have now been synthesized and tested. Structurally the novel 2-ethylidene analogs belong to a class of 19-nor vitamin D compounds characterized by the general formula I shown below: ##STR00001## where Y.sub.1 and Y.sub.2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, and where the group R represents any of the typical side chains known for vitamin D type compounds.

Brief Summary Text (16):
The above novel compounds exhibit a desired, and highly advantageous, pattern of biological activity. The synthesized vitamins were tested for their ability to bind the porcine intestinal vitamin D receptor. The presented results (FIG. 5) indicate that 2-ethylidene-19-norvitamins, possessing methyl group from ethylidene moiety directed toward C-3, i.e., trans in relation to C(6) C(7) bond (isomers E), are more active than 1.alpha.,25-(OH).sub.2D.sub.3 in binding to VDR, whereas their counterparts with cis relationship between ethylidene methyl substituent and C(7)-H group (isomers Z) exhibit significantly reduced affinity for the receptor. The competitive binding analysis showed also that 2.alpha.-ethyl-19-norvitamins bind to the receptor better than their isomers with 2.beta.-ethyl substituents (FIG. 6). In the next assay, the cellular activity of the synthesized compounds was established by studying their ability to induce differentiation of human promyelocyte HL-60 cells into monocytes. E isomer of (20S)-2-ethylidene-19-norvitamin D.sub.3 (FIG. 7) and both 2.alpha.-ethyl-19-norvitamins (FIG. 8) are more potent than 1.alpha.,25-

(OH).sub.2D.sub.3 in this assay, whereas the remaining tested compounds are almost equivalent to the hormone 1. Both E isomers of 2-ethylidene-19-norvitamins, when tested in vivo in rats (Table 1) exhibited very high calcemic activity, the (20S)-compound being especially potent. On the contrary, isomeric Z compounds are significantly less active. 2-Ethyl-19-norvitamins have some ability to mobilize calcium from bone but not to the extent of the hormone 1, while being inactive in intestine. The only exception is the 2.alpha.-ethyl isomer from the 20S-series which shows strong calcium mobilization response and marked intestinal activity.

Brief Summary Text (21):
This invention also provides a novel synthesis for the production of the end products of structures I and II. Two different synthetic paths were devised, both based on Lythgoe type Wittig-Horner coupling of the A-ring fragments, the corresponding phosphine oxides prepared from quinic acid, with the protected 25-hydroxy Grundmann's ketone. In the first method, the allylic phosphine oxides were substituted at C-4' with the ethylidene group whereas in the alternative approach the introduction of ethylidene moiety was performed in the final step of the synthesis, by Wittig reaction of the intermediate 2-oxo-vitamin D analog. The selective catalytic hydrogenation of 2-ethylidene analogs of 1.alpha.,25-dihydroxy-19-norvitamin D.sub.3 provided the corresponding 2.alpha.- and 2.beta.-ethyl compounds.

Description Paragraph (2):
FIG. 1 illustrates the general structural formulae for 1.alpha.,25-dihydroxyvitamin D.sub.3, 1.alpha.,25-dihydroxy-2-methylene-1- 9-norvitamin D.sub.3, and 1.alpha.,25-dihydroxy-2.alpha.-methyl-19-norvita- min D.sub.3, and further illustrates the general structural formulae for the four 2-ethylidene-19-nor-vitamins and the four 2-ethyl-19-nor-vitamins of the present invention synthesized and tested herein;

Description Paragraph (3):
FIG. 2 illustrates the configurations and preferred conformations of the 4'-ethylidene intermediates 16 and 17 used in the synthesis disclosed herein;

Description Paragraph (6):
FIG. 3c illustrates that a strong interaction (designated as A.sup.(1,3)-strain) exists between the methyl group from the ethylidene moiety and equatorial hydroxyls at C-1 or C-3, and results in a strong bias toward conformers with an axial orientation of this hydroxy group to which the methyl from ethylidene fragment is directed; and

Description Paragraph (8):
FIG. 5a is a graph illustrating the relative activity of a 2-ethylidene-19-nor-vitamins (isomers E and Z) and 1.alpha.,25-dihydroxyvitamin D.sub.3 to compete for binding of [.sup.3H]-1,25-(OH).sub.2-D.sub.3 to the pig intestinal nuclear vitamin D receptor;

Description Paragraph (10):
FIG. 6a is a graph illustrating the percent HL-60 cell differentiation as a function of the concentration of the 2-ethylidene-19-nor-vitamins as compared to 1.alpha.,25-dihydroxyvitamin D.sub.3; and

Description Paragraph (16):
In the following lists of compounds, the particular isometric form of the ethylidene substituent attached at the carbon 2 position should be added to the nomenclature. For example, if the methyl group of the ethylidene substituent is in its (E) configuration, then the term "2(E)" should be included in each of the named compounds. If the methyl group of the ethylidene substituent is in its (Z) configuration, then the term "2(Z)" should be included in each of the named compounds. In addition, if the methyl group attached at the carbon 20 position is

in its epi or unnatural configuration, the term "20(S)" or "20-epi" should be included in each of the following named compounds. Also, if the side chain contains an oxygen atom substituted at any of positions 20, 22 or 23, the term "20-oxa", "22-oxa" or "23-oxa", respectively, should be added to the named compound. The named compounds could also be of the vitamin D.sub.2 or D.sub.4 type if desired.

Description Paragraph (17):
Specific and preferred examples of the 2-ethylidene-compounds of structure I when the side chain is unsaturated are:

Description Paragraph (18):
2-ethylidene-19-nor-1,25-dihydroxy-22,23-dehydrovitamin D.sub.3;

Description Paragraph (19):
2-ethylidene-19-nor-24-homo-1,25-dihydroxy-22,23-dehydrovitamin D.sub.3;

Description Paragraph (20):
2-ethylidene-19-nor-24-dihomo-1,25-dihydroxy-22,23-dehydrovitamin D.sub.3;

Description Paragraph (21):
2-ethylidene-19-nor-24-trihomo-1,25-dihydroxy-22,23-dehydrovitamin D.sub.3;

Description Paragraph (22):
2-ethylidene-19-nor-26,27-dimethyl-24-homo-1,25-dihydroxy-22,23-dehydro vit- amin D.sub.3;

Description Paragraph (23):
2-ethylidene-19-nor-26,27-dimethyl-24-dihomo-1,25-dihydroxy-22,23-dehyd rov- itamin D.sub.3;

Description Paragraph (24):
2-ethylidene-19-nor-26,27-dimethyl-24-trihomo-1,25-dihydroxy-22,23-dehy dro- vitamin D.sub.3;

Description Paragraph (25):
2-ethylidene-19-nor-26,27-diethyl-24-homo-1,25-dihydroxy-22,23-dehydrov ita- min D.sub.3;

Description Paragraph (26):
2-ethylidene-19-nor-26,27-diethyl-24-dihomo-1,25-dihydroxy-22,23-dehydr ovi- tamin D.sub.3;

Description Paragraph (27):
2-ethylidene-19-nor-26,27-diethyl-24-trihomo-1,25-dihydroxy-22,23-dehyd rov- itamin D.sub.3;

Description Paragraph (28):
2-ethylidene-19-nor-26,27-dipropoyl-24-homo-1,25-dihydroxy-22,23-dehydr ovi- tamin D.sub.3;

Description Paragraph (29):
2-ethylidene-19-nor-26,27-dipropyl-24-dihomo-1,25-dihydroxy-22,23-dehyd rov- itamin D.sub.3; and

Description Paragraph (30):
2-ethylidene-19-nor-26,27-dipropyl-24-trihomo-1,25-dihydroxy-22,23-dehy dro- vitamin D.sub.3.

Description Paragraph (31):
With respect to the above unsaturated compounds, it should be noted that the double

bond located between the 22 and 23 carbon atoms in the side chain may be in either the (E) or (Z) configuration. Accordingly, depending upon the configuration, the term "22,23(E)" or "22,23(Z)" should be included in each of the above named compounds. Also, it is common to designate the double bond located between the 22 and 23 carbon atoms with the designation ".DELTA..sup.22". Thus, for example, the first named compound above could also be written as 2-ethylidene-19-nor-22,23(E-)-.DELTA..sup.22-1,25-(OH).sub.2D.sub.3 where the double bond is in the (E) configuration. Similarly, if the methyl group attached at carbon 20 is in the unnatural configuration, this compound could be written as 2-ethylidene-19-nor-20(S)-22,23(E)-.DELTA..sup.22-1,25-(OH).sub.2D.sub.3.

Description Paragraph (32):
Specific and preferred examples of the 2-ethylidene-compounds of structure I when the side chain is saturated are:

Description Paragraph (33):
2-ethylidene-19-nor-1,25-dihydroxyvitamin D.sub.3;

Description Paragraph (34):
2-ethylidene-19-nor-24-homo-1,25-dihydroxyvitamin D.sub.3;

Description Paragraph (35):
2-ethylidene-19-nor-24-dihomo-1,25-dihydroxyvitamin D.sub.3;

Description Paragraph (36):
2-ethylidene-19-nor-24-trihomo-1,25-dihydroxyvitamin D.sub.3;

Description Paragraph (37):
2-ethylidene-19-nor-26,27-dimethyl-24-homo-1,25-dihydroxyvitamin D.sub.3;

Description Paragraph (38):
2-ethylidene-19-nor-26,27-dimethyl-24-dihomo-1,25-dihydroxyvitamin D.sub.3;

Description Paragraph (39):
2-ethylidene-19-nor-26,27-dimethyl-24-trihomo-1,25-dihydroxyvitamin D.sub.3;

Description Paragraph (40):
2-ethylidene-19-nor-26,27-diethyl-24-homo-1,25-dihydroxyvitamin D.sub.3;

Description Paragraph (41):
2-ethylidene-19-nor-26,27-diethyl-24-dihomo-1,25-dihydroxyvitamin D.sub.3;

Description Paragraph (42):
2-ethylidene-19-nor-26,27-diethyl-24-trihomo-1,25-dihydroxyvitamin D.sub.3;

Description Paragraph (43):
2-ethylidene-19-nor-26,27-dipropyl-24-homo-1,25-dihydroxyvitamin D.sub.3;

Description Paragraph (44):
2-ethylidene-19-nor-26,27-dipropyl-24-dihomo-1,25-dihydroxyvitamin D.sub.3; and

Description Paragraph (45):
2-ethylidene-19-nor-26,27-dipropyl-24-trihomo-1,25-dihydroxyvitamin D.sub.3.

Description Paragraph (47):
19-nor-2(E)-ethylidene-1.alpha.,25-dihydroxyvitamin D.sub.3;

Description Paragraph (48):
19-nor-2(Z)-ethylidene-1.alpha.,25-dihydroxyvitamin D.sub.3;

Description Paragraph (49):
19-nor-2(E)-ethylidene-20(S)-1.alpha.,25-dihydroxyvitamin D.sub.3; and

Description Paragraph (50):
19-nor-2(Z)-ethylidene-20(S)-1.alpha.,25-dihydroxyvitamin D.sub.3.

Description Paragraph (86):
The preparation of 2-ethylidene-19-nor-vitamin D compounds, and the 2-ethyl-19-nor-vitamin D compounds, having the basic structure I and II can be accomplished by a common general method, i.e. the condensation of a bicyclic Windaus-Grundmann type ketone III with the allylic phosphine oxide IVa or IVb to the corresponding 2-ethylidene-19-nor-vitamin D analogs Va or Vb, respectively followed by a selective reduction of the ethylidene group at C-2 to the corresponding 2-ethyl compounds. ##STR00007## In the structures III, IV, and V groups Y.sub.1 and Y.sub.2 and R represent groups defined above; Y.sub.1 and Y.sub.2 are preferably hydroxy-protecting groups, it being also understood that any functionalities in R that might be sensitive, or that interfere with the condensation reaction, be suitable protected as is well-known in the art. The process shown above represents an application of the convergent synthesis concept, which has been applied effectively for the preparation of vitamin D compounds [e.g. Lythgoe et al., J. Chem. Soc. Perkin Trans. I, 590 (1978); Lythgoe, Chem. Soc. Rev. 9, 449 (1983); Toh et al., J. Org. Chem. 48, 1414 (1983); Baggiolini et al., J. Org. Chem. 51, 3098 (1986); Sardina et al., J. Org. Chem. 51, 1264 (1986); J. Org. Chem. 51, 1269 (1986); DeLuca et al., U.S. Pat. No. 5,086,191; DeLuca et al., U.S. Pat. No. 5,536,713].

Description Paragraph (89):
Referring now to Scheme 2, the next step of the synthesis comprises the Wittig reaction of the sterically hindered 4-keto compound 13 with ylide prepared from ethyltriphenylphosphonium bromide and n-butyllithium leading to ethylidene compounds 14 and 15. Ethylidene compounds 14 and 15 in turn were treated with diisobutylaluminum hydride and the formed alcohols 16 and 17 were in turn transformed to the desired A-ring phosphine oxides 18 and 19. Conversion of 16 and 17, to 18 and 19, respectively involved 3 steps, namely, in situ tosylation with n-butyllithium and p-toluenesulfonyl chloride, followed by reaction with diphenylphosphine lithium salt and oxidation with hydrogen peroxide.

Description Paragraph (90):
Several 2-ethylidene-19-nor-vitamin D compounds of the general structure V may be synthesized using the A-ring synthons 18 and 19 and the appropriate Windaus-Grundmann ketone III having the desired side chain structure. Thus, for example, Scheme 3 illustrates that Wittig-Horner coupling of the phosphinoxy 18 with the protected 25-hydroxy Grundmann's ketone 20 prepared according to published procedure [Sicinski et al., J. Med. Chem. 37, 3730 (1994)] gave the expected protected vitamin compound 21. This, after deprotection afforded 1.alpha.,25-dihydroxy-2(E)-ethylide- ne-19-nor-vitamin D.sub.3 (4a). Similarly, Scheme 3 illustrates the synthesis of 1.alpha.,25-dihydroxy-2(Z)-ethylidene-19-nor-vitamin D.sub.3(5a) from phosphinoxy 19 and Grundmann's ketone 20.

Description Paragraph (91):
Referring now to Scheme 6, the final step of the process was the selective homogeneous catalytic hydrogenation of the ethylidene unit at carbon 2 in the vitamins 4a and Sa performed efficiently in the presence of tris (triphenylphosphine)rhodium(I) chloride [Wilkinson's catalyst, (Ph.sub.3P).sub.3RhCl]. Such reduction conditions allowed to reduce only C(2) =CH.sub.2 unit leaving C(5) C(8) butadiene moiety unaffected. The isolated material is an epimeric mixture (ca. 1:1) of 2-ethyl-19-nor-vitamins 6a and 7a differing in configuration at C-2. The mixture can be used without separation or, if desired, the individual 2.alpha.- and 2.beta.-isomers can be separated by an efficient HPLC system.

Description Paragraph (92):
The C-20 epimerization may be accomplished by the analogous coupling of the phosphine oxides 18 and 19 with protected 20(S)-25-hydroxy Grundmann's ketone 26 (Scheme 5) which after hydrolysis of the hydroxy-protecting groups gave 20(S)-1.alpha.,25-dihydroxy-2-ethylidene-1- 9-nor-vitamin D.sub.3 compounds 4b and 5b. Hydrogenation of 4b and 5b provided the expected mixture of the 2-ethyl-19-nor-vitamin D analogs 6b and 7b.

Description Paragraph (93):
As noted above, other 2-ethylidene and 2-ethyl-19-nor-vitamin D analogs may be synthesized by the method disclosed herein. For example, 1.alpha.-hydroxy-2-ethylidene-19-nor-vitamin D.sub.3 can be obtained by providing the Grundmann's ketone (g). Subsequent reduction of the A-ring ethylidene group in the formed compound can also give the corresponding epimeric mixture of 1.alpha.-hydroxy-2-ethyl-19-nor-vitamin D.sub.3 compounds.

Description Paragraph (98):
The strategy of the synthesis of 2-substituted 19-norvitamins was based on Lythgoe-type Wittig-Horner coupling. Since the corresponding C,D-ring ketones were available, attention was focused on the synthesis of the phosphine oxide A-ring synthons (Scheme 1 and 2). Configurations of the ethylidene unit at C'-4 in the isomeric compounds 16, 17 (FIG. 2) and 17, 18, as well as their preferred conformations, were determined by analysis of .sup.1H NMR spectra, NOE measurements and spin decoupling experiments.

Description Paragraph (99):
The Wittig-Horner reaction of the conjugate base of 20 with the protected 25-hydroxy Grundmann's ketone 20 produced 19-norvitamin D compound 21 in a very high yield, i.e. 91% (Scheme 3), but the yield of an analogous coupling of the isomeric phosphine oxide 19 was very low, i.e. 13%. The obtained condensation products 21 and 22, following deprotection, gave 2-ethylidene-19-norvitamins 4a and 5a. Considering the low yield of the Wittig reaction of the cyclohexanone 13, leading to ethylidene compounds 14 and 15 (Scheme 2), an alternative synthetic approach was sought.

Description Paragraph (100):
Thus, the carbonyl group in 13 was protected as O-trimethylsilyl hemimethylthioketal and the corresponding phosphine oxides 25 were efficiently synthesized (Scheme 4). Coupling of their anions with the hydrindanone 26 (Scheme 5) afforded the protected 19-norvitamin D compound 27 in a high yield. This, after deprotection of 2-oxo group, Wittig reaction and subsequent hydrolysis was converted to (20S)-2-ethylidene-19-norvitamins 4b and 5b. The selective catalytic hydrogenation of 2-ethylidene analogs 4a, b and 5a, b (Scheme 6) provided the corresponding 2-ethyl-19-norvitamins 6a, b and 7a, b, which were easily separated by HPLC.

Description Paragraph (104):
It has been established that vitamin D compounds in solutions exist as a mixture of two rapidly equilibrating A-ring chair conformers abbreviated as .alpha.- and .beta.-forms (FIG. 3a). Presence of bulky 2-alkyl substituents, characterized by large conformational free energy A values (FIG. 3b), shifts the A-ring conformational equilibrium of the synthesized 2-ethyl-19-norvitamins toward the conformers with the equatorial C(2)-substituents. In the obtained 2-ethylidene-19-norvitamin D compounds, an additional strong interaction (designated as A.sup.(1,3)-strain, FIG. 3c) is involved, existing between the methyl group from the ethylidene moiety and equatorial hydroxyls at C-1 or C-3. It results in the strong bias toward conformers with an axial orientation of this hydroxy group to which the methyl from ethylidene fragment is directed.

Description Paragraph (108):

The synthesized vitamins were tested for their ability to bind the porcine intestinal vitamin D receptor. The presented results (FIG. 5a) indicate that 2-ethylidene-19-norvitamins, possessing methyl group from ethylidene moiety directed toward C-3, i.e. trans in relation to C(6) C(7) bond (isomers E), are more active than 1.alpha.,25-(OH).sub.2D.sub.3 in binding to VDR, whereas their counterparts with cis relationship between ethylidene methyl substituent and C(7)-H group (isomers Z) exhibit significantly reduced affinity for the receptor. The competitive binding analysis showed also that 2.alpha.-ethyl-19-norvitamins bind the receptor better than their isomers with 2.beta.-ethyl substituents (FIG. 5b). In the next assay, the cellular activity of the synthesized compounds was established by studying their ability to induce differentiation of human promyelocyte HL-60 cells into monocytes. E isomer of (20S)-2-ethylidene-19-norvitamin D.sub.3 (FIG. 6a) and both 2.alpha.-ethyl-19-norvitamins (FIG. 6b) are more potent than 1.alpha.,25-(OH).sub.2D.sub.3 in this assay, whereas the remaining tested compounds are almost equivalent to the hormone.

Description Paragraph (109):
Both E isomers of 2-ethylidene-19-norvitamins, when tested in vivo in rats (Table 1) exhibited very high calcemic activity, the (20S)-compound being especially potent. On the contrary, isomeric Z compounds are significantly less active. 2-ethyl-19-norvitamins have some ability to mobilize calcium from bone but not to the extent of the hormone 1, while being inactive in intestine. The only exception is 2.alpha.-ethyl isomer from 20S-series that shows strong calcium mobilization response and marked intestinal activity.

Description Paragraph (110):
TABLE-US-00001 TABLE 1 Support of Intestinal Calcium Transport and Bone Calcium Mobilization By 2-Substituted Analogs of 1.alpha.,25-Dihydroxy-19-norvitamin D.sub.3 In Vitamin D-Deficient Rats on a Low-Calcium Diet.sup.a Ca compd. amount transport S/M Serum Ca compound no. (pmol) (mean .+-. SEM) (mean .+-. SEM) none (control) 0 3.0 .+-. 0.7 4.3 .+-. 0.1 1.alpha.,25-(OH).sub.2D.sub.3 1 130 5.5 .+-. 0.5 5.1 .+-. 0.3 260 5.9 .+-. 0.4 5.8 .+-. 0.3 2-ethylidene-19-nor- 4a 65 5.0 .+-. 0.4 4.5 .+-. 0.1 1.alpha.,25-(OH).sub.2D.sub.3 130 6.8 .+-. 0.4 5.2 .+-. 0.2 (E-isomer) 2-ethylidene-19-nor- 5a 65 4.4 .+-. 0.4 4.4 .+-. 0.2 1.alpha.,25-(OH).sub.2D.sub.3 130 5.7 .+-. 0.9 4.2 .+-. 0.0 (Z-isomer) none (control) 0 4.4 .+-. 0.2 4.1 .+-. 0.2 1.alpha.,25-(OH).sub.2D.sub.3 1 130 4.9 .+-. 0.7 5.2 .+-. 0.2 260 6.0 .+-. 0.9 6.4 .+-. 0.4 2-ethylidene-19-nor- 4b 65 9.0 .+-. 0.3 8.2 .+-. 0.3 (20S)-1.alpha.,25- 130 5.8 .+-. 0.8 12.1 .+-. 0.6 (OH).sub.2D.sub.3 (E-isomer) 2-ethylidene-19-nor- 5b 65 4.3 .+-. 0.7 4.0 .+-. 0.3 (20S)-1.alpha.,25- 130 3.8 .+-. 0.3 4.0 .+-. 0.1 (OH).sub.2D.sub.3 (Z-isomer) none (control) 0 3.8 .+-. 0.4 3.9 .+-. 0.1 1.alpha.,25-(OH).sub.2D.sub.3 1 260 6.5 .+-. 0.9 5.8 .+-. 0.1 2.alpha.-ethyl-19-nor- 6a 260 4.0 .+-. 0.4 5.1 .+-. 0.1 1.alpha.,25-(OH).sub.2D.sub.3 2.beta.-ethyl-19-nor- 7a 260 3.7 .+-. 0.3 5.0 .+-. 0.1 1.alpha.,25-(OH).sub.2D.sub.3 2.alpha.-ethyl-19-nor- 6b 260 5.0 .+-. 0.4 7.0 .+-. 0.1 (20S)-1.alpha.,25-(OH).sub.2D.sub.3 2.beta.-ethyl-19-nor- 7b 260 4.1 .+-. 0.3 5.6 .+-. 0.1 (20S)-1.alpha.,25- (OH).sub.2D.sub.3 .sup.aWeanling male rats were maintained on a 0.47% Ca diet for one week and then switched to a low-calcium diet containing 0.02% Ca for an additional three weeks. During the last week, they were dosed daily with the appropriate vitamin D compound for seven consecutive days. All doses were administered intraperitoneally in 0.1 mL propylene glycol/ethanol (95:5). Controls received the vehicle. Determinations were made 24 hours after the last dose. There were at least six rats per group.

Other Reference Publication (11):
Sicinski, Rafal R. et al, "New 1.alpha.,25-Dihydroxy-19-norvitamin D.sub.3 Compounds of High Biological Activity: Synthesis and Biological Evaluation of 2-Hydroxymethyl, 2-Methyl, and 2-Methylene Analogues," J. Med. Chem., 1998, 41, pp. 4662-4672. cited by other

CLAIMS:

1. A method of treating a metabolic bone disease where it is desired to maintain or increase bone mass comprising administering to a patient with said disease an effective amount of a compound selected from the group consisting of 19-nor-2.alpha.-ethyl-1.alpha.,25-dihydroxyvitamin D.sub.3, 19-nor-2.beta.-ethyl-1.alpha.,25-dihydroxyvitamin D.sub.3, 19-nor-20(S)-2.alpha.-ethyl-1.alpha.,25-dihydroxyvitamin D.sub.3, 19-nor-20(S)-2.beta.-ethyl-1.alpha.,25-dihydroxyvitamin D.sub.3, 19-nor-2(E)-ethylidene-1.alpha.,25-dihydroxyvitamin D.sub.3, 19-nor-2(Z)-ethylidene-1.alpha.,25-dihydroxyvitamin D.sub.3, 19-nor-2(E)-ethylidene-20(S)-1.alpha.,25-dihydroxyvitamin D.sub.3, 19-nor-2(Z)-ethylidene-20(S)-1.alpha.,25-dihydroxyvitamin D.sub.3.

16. The method of claim 1 wherein the compound is 19-nor-2(E)-ethylidene--1.alpha.,25-dihydroxyvitamin D.sub.3.

17. The method of claim 1 wherein the compound is 19-nor-2(Z)-ethylidene--1.alpha.,25-dihydroxyvitamin D.sub.3.

18. The method of claim 1 wherein the compound is 19-nor-2(E)-ethylidene-- 20(S)-1.alpha.,25-dihydroxyvitamin D.sub.3.

19. The method of claim 1 wherein the compound is 19-nor-2(Z)-ethylidene-- 20(S)-1.alpha.,25-dihydroxyvitamin D.sub.3.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 4. Document ID: US 20050043281 A1 Relevance Rank: 94

L3: Entry 4 of 10 File: PGPB Feb 24, 2005

PGPUB-DOCUMENT-NUMBER: 20050043281
PGPUB-FILING-TYPE: new
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TITLE: 2-Ethyl and 2-ethylidene-19-nor-vitamin D compounds

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 5. Document ID: US 20050282789 A1 Relevance Rank: 94

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PGPUB-DOCUMENT-NUMBER: 20050282789
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TITLE: 2-ethyl and 2-ethylidene-19-nor-vitamin D compounds

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☑ 6. Document ID: MX 234634 B, WO 200192221 A1, AU 200165272 A, US 20030013691 A1, EP 1286962 A1, BR 200111173 A, JP 2004501114 W, MX 2002011820 A1, NZ 522909 A, US 6806262 B2, US 20050043281 A1, EP 1524264 A2, US 20050282789 A1, US 6992074 B2 Relevance Rank: 87

L3: Entry 10 of 10 File: DWPI Mar 2, 2006

DERWENT-ACC-NO: 2002-097754
DERWENT-WEEK: 200651
COPYRIGHT 2006 DERWENT INFORMATION LTD
TITLE: New 2-ethyl and 2-ethylidene-19-nor-vitamin D derivatives, useful for treating e.g. metabolic bone diseases, psoriasis, cancerous diseases, rheumatoid arthritis, alopecia, skin conditions, hypertension or hypocalcemia

INVENTOR: DELUCA, H F; SICINSKI, R R

PRIORITY-DATA: 2000US-208199P (May 31, 2000), 2001US-0871227 (May 31, 2001), 2004US-0957483 (October 1, 2004), 2005US-0191791 (July 28, 2005)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
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WO 200192221 A1	December 6, 2001	E	058	C07C401/00
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US 20050043281 A1	February 24, 2005		000	A61K031/59
EP 1524264 A2	April 20, 2005	E	000	C07C401/00
US 20050282789 A1	December 22, 2005		000	C07C401/00
US 6992074 B2	January 31, 2006		000	A61K031/59

INT-CL (IPC): A61K 31/59; A61K 31/593; A61P 1/00; A61P 3/10; A61P 5/18; A61P 7/00; A61P 9/10; A61P 9/12; A61P 13/08; A61P 15/00; A61P 17/00; A61P 17/06; A61P 17/14; A61P 19/00; A61P 19/02; A61P 19/10; A61P 25/00; A61P 29/00; A61P 35/02; A61P 37/06; C07C 401/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☑ 7. Document ID: US 20060160779 A1 Relevance Rank: 87

L3: Entry 1 of 10 File: PGPB Jul 20, 2006

PGPUB-DOCUMENT-NUMBER: 20060160779
PGPUB-FILING-TYPE:
DOCUMENT-IDENTIFIER: US 20060160779 A1

TITLE: 2,2-Di-substituted 1alpha,25-dihydroxy-19-norvitamin d derivative

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 8. Document ID: US 20040229851 A1 Relevance Rank: 87

L3: Entry 5 of 10 File: PGPB Nov 18, 2004

PGPUB-DOCUMENT-NUMBER: 20040229851
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040229851 A1

TITLE: 2-Propylidene-19-nor-vitamin D compounds

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☑ 9. Document ID: EP 1524264 A2 Relevance Rank: 87

L3: Entry 9 of 10 File: EPAB Apr 20, 2005

PUB-NO: EP001524264A2
DOCUMENT-IDENTIFIER: EP 1524264 A2
TITLE: 2-ethylidene-19-nor-vitamin D compounds

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 10. Document ID: US 20060078903 A1 Relevance Rank: 87

L3: Entry 2 of 10 File: PGPB Apr 13, 2006

PGPUB-DOCUMENT-NUMBER: 20060078903
PGPUB-FILING-TYPE:
DOCUMENT-IDENTIFIER: US 20060078903 A1

TITLE: Methods and compositions for the diagnosis and treatment of cyclin A-1 associated conditions

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Terms	Documents
SICINSKI and ethylidene	10

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